DOCTORAL THESIS

Neuroprotective effects and underlying mechanisms of Chinese medicinal compounds in Parkinson's disease models

Lu, Jiahong

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Neuroprotective Effects and Underlying Mechanisms of Chinese Medicinal Compounds in Parkinson's Disease Models

LU Jiahong

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Principal Supervisor: Dr. Li Min

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting 2% of the population over 65 years old. The biochemical and molecular mechanisms leading to dopaminergic neuronal degeneration in PD remain unclear. However, a large body of evidence suggests that oxidative stress and abnormal protein aggregation are two critical factors contributing to the pathogenesis of PD.

6-Hydroxydopamine (6-OHDA), an analog of the neurotransmitter dopamine, is widely used to induce PD-like damages in animals as well as in cells, and has been used to test neuroprotective effects of multiple anti-PD drugs. In this study, 6-OHDA was used to induce SH-SY5Y cells toxicity as a cellular PD model for the screening of anti-PD compounds derived from Chinese herbal medicines. Our study revealed that baicalein, a flavonoid extracted from Chinese herbal medicine Huangqin (*Scutellaria baicalensis* Georgi), inhibited 6-OHDA-induced cell death in human neuroblastoma SH-SY5Y cells, probably via stabilizing the intracellular calcium homeostasis.

Abnormal protein aggregation and accumulation in the brain have been linked to the pathogenesis of neurodegenerative diseases including PD. Recent studies suggested that the oligomeric form of aggregates may represent the most toxic species, and thus could be a good therapeutic target. Our study revealed that baicalein inhibited both oligomerization and fibrillation of alpha-synuclein (α-syn) *in vitro* and prevented the formation of α-syn oligomers in neuronal cells. Baicalein also protected SH-SY5Y cells from α-syn oligomer-induced toxicity. Our study indicates that baicalein is a good inhibitor of α-syn aggregation and toxicity.

One of the strategies for the treatment of neurodegenerative diseases is to promote the clearance of abnormal protein aggregates in the neurons. Autophagy-lysosome system is a major mechanism for the degradation of large protein aggregates in the cells, thus

seeking potent autophagy enhancers to promote the degradation of pathogenic protein aggregates could be a strategy to identify therapeutic agents for neurodegenerative diseases. Our study identified a potent autophagy inducer-isorhynchophylline (IsoRhy), an alkaloid isolated from herbal medicine Gouteng (*Uncaria rhynchophylla*（Miq.）Jacks). IsoRhy induced massive autophagy in neuronal cells (N2a, SH-SY5Y, PC12 and primary neuron) as well as in the brain of *Drosophila*; IsoRhy promoted degradation of wild type & mutant alpha–synuclein monomers, alpha–synuclein oligomers and alpha–synuclein/synphilin-1 aggresomes in neuronal cells via autophagy-lysosome pathway; IsoRhy Induced autophagy in N2a cells in a mTOR-independent but beclin-1-dependent manner.

Given the role of oxidative stress and abnormal protein aggregation in neurodegenerative diseases including PD, our results suggest that baicalein and IsoRhy, the bioactive compounds isolated from Chinese herbal medicine, may have potential to be developed into therapeutic agents for the treatment of these devastating disorders.

Keywords: Abnormal protein aggregation, Alpha-synuclein, Autophagy, Baicalein, Isorhynchophylline, Parkinson’s disease, 6-hydroxydopamine,

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